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The course of schizophrenic psychoses: what do we really know? A selective review from an epidemiological perspective

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Abstract There is only a limited amount of definite knowledge on the course of schizophrenic psychoses, although 100 years have passed since they were first described by Kraepelin as "Dementia praecox". The main reason for this is that most studies done thus far suffer from more or less serious methodological shortcomings: samples were often highly selective; investigations were often not direct, not prospective and almost never continuous, which would be of utmost importance in an episodic disease such as schizophrenia; assessments in older studies were neither standardized nor tested for validity or reliability; in more recent studies they were often not conducted by experienced psychiatrists; patients who refused to participate or who died during the study period were widely neglected. Nevertheless, we have learned that schizophrenic psychoses do not have a steadily deteriorating course ending in "dementia". On the contrary, the course of these psychoses seems very heterogeneous. Due to their methodological shortcomings, studies done thus far even seem to have underestimated heterogeneity by partly neglecting patients with very good outcome, on the one hand, and very poor outcome, on the other hand.

Key words Schizophrenia · Course · Follow-up studies · Methodology · Predictors

Introduction

The syndrome which we presently call schizophrenia was described as an entity for the first time in 1896 by Kraepelin. He initially named the illness "Dementia praecox", "premature dementia", thereby expressing a very pessimistic view of the course of this disease. At that time he was of the opinion that the illness follows a path of continuous progression with persistent and most serious symptomatology in over 70% of cases.

We now know that this picture was decidedly too pessimistic. For one matter, the illness does not end in dementia. It instead seems that the extremely poor course of cases observed earlier was to a considerable degree a consequence of the long-term hospitalization and the accompanying psychosocial understimulation that these patients underwent. Secondly, it has been shown that there are, indeed, cases of cures, that some patients never become ill again after a single episode or that others, even after many years of chronic illness, can show considerable improvement. With the introduction of neuroleptics in the 1950s and through the development of community-based care, a breakthrough appeared to have been reached bringing lasting positive effects in the short-term and hopefully in the long-term course as well. The initial euphoria has, however, been tempered by partial disillusionment; there are also recent studies which show that schizophrenia still "is a chronic disease, frequently disabling for a lifetime and with an outcome generally worse than that of other functional mental illnesses" (McGlashan 1988).

But how disabling is it really and how often is it disabling? What do we – 100 years after Kraepelin – really know about the course of this disease (or group of diseases) and how well do we know it?

Hegarty et al. (1994) identified a total of 821 studies on the course of schizophrenia conducted worldwide between 1895 and 1992. Of these, however, only 320 satisfied certain methodological standards such as a minimum of 15 patients, no mixing with other diagnostic groups, a minimum observation period of 1 year, dropout rate of under 33%, etc. Further methodological shortcomings have been discussed, e.g. by Retterstøl (1987) and McGlashan et al. (1988).

The purpose of this paper is therefore to review critically what we really know about the course of schizo-

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phrenic psychoses if we selectively look at methodologically sound studies.

Methods

In a first step, an attempt was made to identify all studies on course or outcome of schizophrenic psychoses (excluding treatment studies) published thus far in English or German. Studies published since 1966 were identified through a MEDLINE computerized literature search under the headings "schizophrenia" or "schizophrenic" and "course", "outcome" or "follow-up". All additional references found in these articles as well as in the standard textbooks and handbooks of this century were also examined.

In the second step those studies were selected which satisfied certain methodological standards: prospective, standardized and direct investigation of a representative, catchment-area-based sample of first-admitted or first-contact patients diagnosed directly and according to a standardized diagnostic system.

In the third step the results of the few studies really satisfying these methodological standards were reviewed.

Results

I. Methodological limitations of previous studies

Some of the main problems of previous studies are as follows:

1. Almost all previous studies describe more or less selection-biased patient groups. These studies are often restricted to the patients of a particular hospital or outpatient clinic, and results gathered from selection-biased patient groups do not allow for general statements about the course of schizophrenia. Only recently have follow-up studies with complete population-based samples, i.e. investigating all first-onset patients of a defined catchment area, been initiated.

2. In most studies the course of the disease was by no means observed starting from the first hospital admission, let alone the disease's actual onset. Instead, the cohorts were made up of variously proportioned numbers of first-admitted and re-admitted patients. In these "hospital prevalence samples", however, there is an overrepresentation of chronic cases, because these are either hospitalized long-term or often readmitted (Cohen and Cohen 1984). This means that mainly patients with a poor prognosis are examined, thus presenting a much too negative picture of the course of this disease.

3. A selection of cases with a chronic course is also achieved by adhering to certain diagnostic rules e.g. as in DSM-III and -IV, where schizophrenia can only be diagnosed after at least 6 months of duration of the disease.

4. Often the patients were not examined *directly* until years or even decades after their first hospitalization, i.e. these studies were usually not prospective follow-ups but retrospective "follow-backs". Even among the prospective follow-up studies, often a significant portion of the course of the disease was assessed only retrospectively based on medical records. Some studies even consist exclusively of analyses of medical records.

5. The diagnosis as well, which often can only be made during an acute phase of the illness, was frequently taken from medical records or made retrospectively based on case notes. Apart from that, until the 1970s there were no precisely defined, standardized systems on which to base a diagnosis.

6. In more recent follow-up studies, patients were interviewed directly, but the interviews took place at standardized intervals, leaving to chance whether the patient at the actual time of follow-up examination happened to be in a phase of acute relapse or remission. Such cross-sectional assessments after set time periods do not say much about the course between cross sections and do not really allow for the classification of the course of an episodic disease. Prospective studies which attempt to follow patients closely and record information first-hand through all phases of illness are a rarity.

7. In the older studies neither course nor "outcome" were assessed with standardized instruments. This means that the assessments were often subjective and dependent on the particular observer.

8. The more recent studies were conducted with standardized instruments, but often no mention is made concerning the reliability and validity of the assessments. This is of particular relevance in the more recent studies, because they were often no longer conducted by experienced psychiatrists but only by "trained researchers".

9. Course and "outcome" were judged according to diverse criteria in the various studies. Whereas one study assessed "outcome" according to which symptoms the patient still showed after a certain period of time, another study's criteria had more to do with the quality of the patient's social adjustment, and a third study based its assessment on a global judgement with a mixture of both criteria. Even in studies using the same criteria, the methods were often not the same.

10. In some studies there is a lack of essential information about variables which have a strong bearing on the course of the illness, e.g. age at onset, age at first admission, already existing chronicity at the outset of the study, details about previous treatment, genetic loading, the existence of other potential biological or psychosocial risk factors, comorbidity, etc.

11. The problem of how to deal with study dropouts or missing data has also often not been considered carefully enough. Thus, there are only a few studies which have tested what sort of distortion the results undergo when certain patients – possibly the most severely ill – refuse to continue with the study.

12. Finally, most studies do not adequately take into account the large proportion of patients who die during the observation period. This is especially important because the many patients who commit suicide might be those who are most severely ill.

These are some of the most important methodological shortcomings of many studies conducted so far.

The major studies

Some important though methodologically limited studies. Nevertheless, some of the older studies have important advantages as well: often many patients were directly examined with great psyhiatric experience and over very long periods of time. They have thus been fundamental in shaping the basis of current knowledge and some of them are therefore at least briefly mentioned (Table 1).

At the Zürich University Hospital in the years 1942 and 1943, Manfred Bleuler (1972) studied 208 patients admitted with schizophrenia (first- and re-admittances) whom he treated personally for a period ranging from 5 to 20 years.

Hinterhuber (1973) was one of the first to confine this study to first-admitted patients. He conducted a catamnesis with 157 schizophrenics who had been treated during a 5-year period at the Innsbruck University Hospital 30–40 years after their first admission. Drawing on a variety of information sources, he attempted to reconstruct the course in a very detailed manner, even of those who had died.

In the "Lausanne Study", Ciompi and Müller (1976) studied 289 former patients of the Lausanne University Hospital at their homes. With an average observation period of 37 years, this study ranks as the longest running, but only 18% of the original cohort could be traced.

In the "Bonn Study" Huber et al. (1979) examined 502 patients with first- and re-admissions to the Bonn University Hospital between 1945 and 1959 after an average period of 22 years.

The study conducted by Möller et al. (1982) was one of the first to use standardized instruments. The 103 patients observed, however, as the authors themselves mention, are a selection of patients treated at a certain institute.

In the "Cologne Study" Marneros et al. (1991) studied 148 schizophrenics at an average of 25 years after the disease's first manifestation and compared them with patients with affective, schizoaffective and other disorders. This cohort was highly selected based on psychopathological criteria, chosen from all 1208 first-admitted schizophrenic patients at the Cologne University Hospital between 1950 and 1979.

The largest studies on the course of schizophrenia have thus far been planned and coordinated through the World Health Organization (WHO) in the form of multicentre studies. The "International Pilot Study on Schizophrenia"

Table 1 Some major studies

Reference	Location/name of study	No. of patients	Year(s) of selection[a]	Observation period	Representative sample?	First admitted only?	Prospective?
Bleuler (1972)	Zürich (CH)	208	1942–1943	5–20 years	No	No	No
Hinterhuber (1973)	Innsbruck (A)	157	1930–1940	30–40 years	No	Yes	No
Ciompi and Müller (1976)	Lausanne study (CH)	289	1900–1962	M = 37 years	No	Yes	No
Huber et al. (1979)	Bonn study (BRD)	502	1945–1959	8–28 years (M = 22 years)	No	No	No
WHO (1979)	WHO-IPSS, 8 countries	1202	1960s	5 (10) years	No	No	Yes
Tsuang et al. (1979)	IOWA study (USA)	186	1934–1944	30–40 years	?	No	No
Möller et al. (1982)	Munich (BRD)	103	1972–1974	5 years	No	No	Yes
McGlashan (1984 a, b)	Chestnut-Lodge study (USA)	163	1950–1975[b]	2–32 years (M = 15 years)	No	No[b]	No
Jablensky et al. (1980)	WHO Dis. st.[d] 7 countries	7 × 70	End of 1970s	5 (10) years	No	(Yes)[c]	Yes
Biehl et al. (1986)	WHO Dis. st.[d], subsample Mannheim (BRD)	70	1978	5 years	No	(Yes)[c]	Yes
an der Heiden et al. (1995)	WHO Dis. st.[d], subsample Mannheim (BRD)	56	1978	14 years	No	(Yes)[c]	Yes
Harding et al. (1987 a, b)	Vermont study (USA)	168 (82 as per DSM-III)	ca. 1960[b]	22–62 years (M = 32 years) with 20–25 years prospective	No	No[b]	Yes
Helgason (1990)	Island	107	1966–1967	21-22 years	Yes?	(Yes)[c]	Partially
Johnstone et al. (1986, 1990)	Northwick Park study, (UK)	253	1979–1981	2 years	No	(Yes)[c]	Yes
Johnstone et al. (1991)	Harrow, London (UK)	532	1975–1984	5–15 years	No	No	No
Marneros et al. (1991)	Cologne study (BRD)	148	1950–1979	M = 25 years	No	Yes	No

[a] If not noted otherwise, patients examined were hospitalized in the respective years
[b] Patients examined were discharged in the respective years
[c] Patients examined had first out- or inpatient contact in the respective years
[d] *Dis. st.* Disability study

(IPSS), a transcultural examination of a total of 1202 patients in eight countries, was begun in the 1960s (WHO 1979). Emphasis was placed on developing methodology for future studies; thus, representative samples were not yet studied.

In the WHO "Disability Study" (Jablensky et al. 1980) some centres came closer to representativity. In Mannheim, Biehl et al. (1986) studied all 70 patients with in- or outpatient contact to one of three main treatment centres in a particular catchment area prospectively over a period of 5 years. An der Heiden et al. (1995) have in the meantime conducted a 14-year follow-up. But since outpatient first-contacts to psychiatrists in office practice and other institutions were not included, this was not strictly a sample of first-contact patients. A criterion of the study was "onset of illness not more than 1 year prior to inclusion", which possibly resulted in a further selection of patients with a relatively good prognosis. We now know that psychotic symptoms begin on average approximately 2 years prior to the first hospitalization with the diagnosis of schizophrenia (Häfner et al. 1991) and patients with a longer period of illness prior to first treatment are probably often those with a poorer prognosis (Crow et al. 1986).

Some recent great North American studies with a follow-up of over 10 years and a study population of at least 100 patients are also mentioned:

In the "lowa 500 Study", Tsuang et al. (1979) studied 186 schizophrenic patients over 30–40 years. They retrospectively included all patients who had been treated between 1934 and 1944 in the emergency hospital serving the State of Iowa. Operationalized diagnoses could only be established using medical records. Based on Feighner's very strict criteria (Feighner et al. 1972), two thirds of the original cohort of schizophrenic patients were eliminated leaving only a very narrowly defined group for this follow-up study.

In the "Chestnut Lodge Study", McGlashan (1984a, b) reported on 163 schizophrenic patients who had been *released* from Chestnut Lodge, a private institution for care, over a period of 25 years. The diagnosis and baseline assessments were based on records. Follow-up took place between 2 and 32 years after discharge (average 15 years), in some cases only by telephone and/or interviewing significant others.

The Vermont Study (Harding et al. 1987a, b) was a retrospective investigation starting off with an original cohort of 269 chronic, long-term hospitalized schizophrenics. The patients had been staying in the back wards of Vermont State Hospital. After a rehabilitation program between 1955 and 1960, they were *released* into community-based care. Even after 20–25 years, it was possible to gather information on over 97% of these patients. Of the survivors, 168 were interviewed personally; only 82 of these, however, retrospectively fulfilled DSM-III criteria for schizophrenia.

All these studies, however, suffer more or less from the previously mentioned methodological problems.

The methodologically sound studies. Only few studies could be identified which are not affected by these problems and which especially fulfil the following criteria: prospective, standardized and direct investigation of a representative, catchment-area-based sample of first-admitted or first-contact patients, diagnosed directly and according to a standardized diagnostic system. These studies are shown in Table 2. They are the first to permit a certain amount of generalization about the course of schizophrenic disorders. They are described briefly before a review of their main results.

The first of these more reliable studies is the Buckinghamshire Study by Shepherd et al. (1989), in which all 121 schizophrenics, including 49 first-admitted, of a particular catchment area were studied prospectively over 5 years. This study was the first to apply important epidemiological and methodological considerations such as a set catchment area and time frame with a follow-up phase of exactly 5 years for all patients. Standardized techniques were used for assessing symptomatology and social disability. This study, nevertheless, has certain limitations, discussed in part by Shepherd et al. (1989) themselves. The main limitation is that a sample of only 49 first-admitted patients is too small to allow for very sophisticated statements. In a few cases follow-up was not possible, potentially causing a slight amount of distortion. The patients can also only the considered as representative for the respective studied region, which, for instance, includes no larger industrial crities. Finally, in this study, as in almost all others, only inpatients were included.

Table 2 Methodologically sound studies with representative samples of first-onset patients, standardized diagnosis/assessment and prospective design

Reference	Location/name of study	No. of patients	Year(s) of selection	Duration of follow-up (years)
Shepherd et al. (1989)	Buckinghamshire study, UK	49[b]	1973–1974	5
Häfner et al. (1989)	Case-register study, Denmark	1169[b]	1976	10
Salokangas and Stengård (1990)	Tampere, Finnland	227[c]	1983–1984	2
WHO, Jablensky et al. (1992)	Determinants of Outcome study, 10 countries	1379[c]	1978–1980	2
Häfner et al. (1991, 1993a, b)[a]	ABC study, BRD Rhein-Neckar region	(267[b]) 133[b]	1987–1989	5

[a] Follow-back with $n = 267$ regarding preclinical course, and 5-year follow-up after first admission with a subsample of $n = 133$
[b] First admitted
[c] First contact (out- or inpatient)

Similar criticisms hold for the following epidemiological studies.

Salokangas and Stengård (1990) examined all 227 patients from six districts in Finnland who, during 1 year and for the first time, had sought psychiatric help as outpatients or inpatients.

The largest of these representative studies was again conducted by the WHO in the form of a transcultural study. Twelve centres in ten countries took part in this study on the "Determinants of Outcome of Severe Mental Disorders" (DOS; Jablensky et al. 1992). All first-contact patients of the respective catchment areas were included, those with inpatient as well as those with outpatient contact to a wide variety of facilities, including even traditional healers. Having conducted a wide-ranging screening for patients, it is likely that only very few patients in the initial stages of illness were overlooked, thus providing a representative sample of 1379 patients in the various centres.

Häfner et al. conducted a study at the Central Institute for Mental Health, the ABC study (Age, Beginning and Course of Schizophrenia) in which all 392 patients first admitted with a schizophrenic, paranoid or paranoid reactive psychosis (ICD-9: 295, 297, 298.3 + 4; WHO 1978) of an exactly defined catchment area of approximately 1.5 million inhabitants and of a period of exactly 24 months in the years 1987–1989 were screened. A representative sample of 267 of these patients could be thoroughly studied with standardized instruments (Häfner et al. 1991, 1992, 1993 a, b; Riecher et al. 1989, 1991). The *early* course of the illness, that is *prior* to first hospitalization in which the above-named diagnoses were made, was investigated retrospectively in detail. A representative subsample of 133 patients was then followed-up for 5 years.

Regarding early course before first hospitalization and 10-year course thereafter, analyses based on case register data from Denmark have also been conducted and include all Danish patients first admitted in 1976 with the same diagnostic spectrum as in the ABC study (Häfner et al. 1989, 1991; Riecher et al. 1991; Maurer 1995).

II. What do we really know from these studies?

As outlined, we are confronted with a vast amount of methodologically often not very sound studies. What can we really believe? Which results are valid, reliable and meaningful? The following is an attempt to assess the actual knowledge of the course of schizophrenic disorders with an emphasis on the results of the previously described methodologically sound studies which allow a certain generalization of conclusions.

Results on early course (before first admission)

Until recently, there have not been many studies on the onset and the early course of schizophrenic disorders before the first hospitalization. One of the first studies was by Huber et al. (1979) who in more than one third of their patients found unspecific signs of illness which preceded what is recognized as the actual schizophrenic disorder and which they labelled as "Vorpostensyndrom" (antecedant syndrome) and "prodomi". Also Haas and Sweeney (1992), Loebel et al. (1992) and Beiser et al. (1993) have recently examined the early course of schizophrenia. Basically, they describe an average length of time with prominent psychotic symptoms before treatment or hospitalization of approximately 1 year, and a period with prodromal symptoms of approximately the same length before that.

As part of the previously mentioned ABC study (Häfner et al. 1991; Riecher et al. 1991), a representative cohort of 267 first-admitted patients were interviewed in detail as to the onset of illness and history of mental problems using a standardized instrument constructed especially for this purpose ("IRAOS", Häfner et al. 1992). Additionally, significant others were interviewed and various other sources of information, such as medical records, earlier medical letters, etc., were utilized. Results showed that the first hospitalization in which the respective diagnosis was made had very often been preceded by a long period in which signs of the beginning illness were already identifiable. Calculated from the first sign of a mental disturbance, this period of time averaged at 4.2 years for men and 4.9 years for women. At first these signs were only unspecific indicators, such as loss of energy and motivation, difficulty concentrating, anxiety, suspiciousness and social withdrawal. Often there was an outwardly noticeable turning point after which the patients no longer behaved as they had previously and no longer fulfilled their social roles at work and at homes as they once had. Even the first psychotic symptomatology appeared on average already 2 years prior to the first hospitalization with a diagnosis of schizophrenia or paranoid disorder (Häfner et al. 1991, 1992, 1993 a, b; Riecher et al. 1991).

Many patients obviously make use of outpatient treatment because of these early symptoms. In the previously mentioned Danish case-register study (Riecher et al. 1991; Häfner et al. 1989) 15–25% of patients had even been admitted to hospital already without there having been a diagnosis of schizophrenia at this point. These patients had usually been treated for what was initially diagnosed as a personality disorder, a neurosis or a depressive psychosis until, months or years later, they were readmitted clearly showing schizophrenic symptomatology.

Well in accordance with this, in the WHO's "Determinants of Outcome of Severe Mental Disorders" (DOS; Jablensky et al. 1992) "negative" manifestations, such as neglect of usual activities and loss of appetite, sleep or interest in sex, etc., were more frequently recognized as the first signs of illness than were psychotic symptoms. Family members and other key informants proved themselves to be sensitive observers in this matter.

These studies impressively show that schizophrenia does not start with first admission and not even with the first psychotic symptoms. Obviously one can often notice a marked change in behaviour a long time before actual

onset. This phenomenon was described by earlier German psychiatrists as a "break in the lifeline ("Knick in der Lebenslinie"). The findings imply that it is probably not correct to call these behavioural disturbances "*pre-*"morbid characteristics, as they obviously are not "pre-"existing personality traits, but instead seem to indicate a change, possibly the onset of a pathogenetic process at a very early stage. High-risk studies have also contributed to our knowledge about these early phases of the disease.

Results on further course (after first admission)

In contrast to the studies just presented, most studies, whether prospective or in part retrospective, did not begin examination of the course of illness until after the first hospitalization in which schizophrenia was diagnosed. Course was assessed based on diverse criteria with information gathered on treatment parameters, symptomatology or the different levels of psychological impairment and social disability.

Treatment parameters. Regarding inpatient treatment, the Danish case-register study by Häfner et al. (1991) gives reliable data on all 1169 Danish citizens who were first admitted with schizophrenia or a paranoid psychosis in 1976. During the following 10 years 33% did not have to be rehospitalized. On average, however, within this time period the men had 3.7 hospital stays and the women 3.4 (including first stay). The total time spent in hospital amounted to an average of 486 days for the men and 354 for the women.

Shepherd et al. (1989) found that of their 49 first-admitted patients, 45% did not require further inpatient treatment during a period of 5 years. On average the patients spent approximately 8.5 months in hospital (including first stay), and only two of these patients stayed in hospital almost the entire 5 years. During this time 98% of patients received medication, 39% continuously.

Jablensky et al. (1992) have presented 2-year follow-up results from the WHO DOS study. The starting point for the follow-up were not only inpatient first admissions, but also all first contacts of patients with schizophrenia-like symptomatology in any sort of outpatient or inpatient facility; thus, a very early stage of the disease was being assessed. Of the original 1379 patients, it was possible to reinvestigate 1078, the dropouts not differing significantly from those followed-up in terms of fundamental criteria. Not a single patient had a long-term hospitalization during these 2 years. Of the total population 31% were never hospitalized during these 2 years – however, with a marked variance of 0% in Prague (Czech Republic) and Rochester (USA), and up to 81 and 91%, respectively, in urban and rural regions of India. It is likely that this variance has to do with complex factors such as the availability of beds, culture-specific attitudes toward mental illness, etc., and is not simply a measure of the severity of course. Ninety-five percent of the patients received neuroleptics during this time, patients in industrial countries on average over a longer period of time than those in developing countries, this probably similarly having to do with availability.

Symptomatology. Type and severity of symptomatology are more direct indicators of the severity of course *if* they are assessed continuously and not in arbitrary cross-sections only. A study which continually assessed symptomatology in a sophisticated manner is that of Shepherd et al. (1989). Of his 49 first admitted patients, 22% remained symptom free over the 5 years following the first admission; 35% developed further discrete episodes, but were free of psychotic symptoms between episodes; 8% had persistent florid symptoms with one or more exacerbations and suffered from stable residual psychopathology between episodes; 35% showed the same florid picture with increasing impairment after each episode.

In the WHO DOS study (Jablensky et al. 1992), the majority of patients showed a remittent course during the very early 2-year period of their disease: 50% had only a single psychotic episode, 31% two or more episodes followed by a remission and only 16% displayed lasting psychotic symptomatology without remission. Of all patients, 19% were psychotic only for a "very short" period of time (i.e. less than 5% of the total follow-up period), and 18%, on the other hand, "during almost the entire 2 years" (i.e. more than 75% of the total observation period). However, there seemed to be great variation between the different centres. For example, in Aarhus (Denmark), as little as 28% had only one psychotic episode, whereas the corresponding figure in a rural area of India was 75%. On the other hand, the proportion of patients with lasting psychotic illness varied between only 2% in Ibadan (Nigeria) and as much as 33% in Nagasaki (Japan).

The Nottingham subsample of the DOS study has been followed up over 13 years (Mason et al. 1995, 1996). Of originally 67 schizophrenic patients (ICD-9), 58 could be reassessed, 48 of them directly. Eighteen percent of the sample had never relapsed and 25% were never readmitted. However, 33% of the cohort had experienced psychotic symptoms almost continuously. In the first year the amount of time spent in psychotic episodes and in hospitals was greatest, with social adjustment at its worst. After the initial episode, the course of the disease was relatively stable. At 13-year follow-up 44% of the patients were found to be recovered or only mildly impaired.

On the whole, these studies seem to show that the course of schizophrenic and schizophrenia-like disorders is by no means as bad as some previous studies implied. The sooner in the course of the disease one assesses the patients, the more patients with complete remission can be found.

Social disability. "Social functioning" in the WHO DOS study (Jablensky et al. 1992) was assessed by judging whether a patient was able to fulfil various social and work-related roles as adequately as an average person of the same age and gender, social and educational background and culture. More than one third of patients showed no sign of impairment during at least three quar-

ters of the observation period, and only less than one third suffered more or less severe impairments during the entire 2 years.

Shepherd et al. (1989) rated social impairment after 5 years. Of their patients, 45% showed only minimal impairment, 43% mild to moderate, and 12% severe impairment. In their ability to work, 24% of patients were mildly to moderately impaired and 16% severely impaired; almost half of the patients were mildly to moderately disturbed in their leisure and social skills and 15% severely disturbed; finally, in family relationships there were mild to moderate problems for 36% and severe problems for 14% of the patients.

In the ABC study it was shown that these impairments very often already occur in the early preclinical course of the disease. The consequence of this is that, compared with their contemporaries, these often very young patients frequently lag behind in their social development from the start (Häfner et al. 1995, 1998).

Mortality. Mortality is another important parameter in assessing the course of illness. It is known to be distinctly higher among schizophrenic patients than it is in the general population, especially because of suicide (for review see e.g. Tabbane et al. 1993).

Mortensen and Juel (1993) recently completed a methodically very sound study and came up with very pessimistic results. By linkage of different case registers, they studied all 9156 patients who were first hospitalized in Denmark between 1970 and 1987 and were at some point diagnosed with schizophrenia. The analyses covered a course of several months up to 18 years after first hospitalization. In comparison with the general population of the same age groups, the mortality of the schizophrenic patients was significantly higher: the relative risk was 4.7 for men and 2.3 for women, with the relative risk decreasing with increasing age.

As regards the causes, suicide was accountable for the deaths of 50% of the men and 35% of the women. This means that death from suicide occurred 20 times more frequently for both men and women, as was the case in the general population. The risk of suicide was especially high in the first year of follow-up. But there was also excess mortality from fatal accidents, homicide, and heart and respiratory tract illnesses. The authors attribute this study's very high mortality rates partly to the fact that Denmark has stricter clinical criteria for a schizophrenia diagnosis as compared with other countries. They were, therefore, dealing with a group of relatively severely ill patients. Furthermore, they had only included first-admitted patients in this study, whereas other studies have often analysed a mixed population of first- and readmitted. Since suicide risk is especially high in the first years of illness, the findings of previous studies have obviously been too optimistic (Mortensen and Juel 1993).

Table 3 Frequently found predictors of the course of schizophrenia

Favourable	Unfavourable
High age at onset	Early onset
Female gender	Male gender
Married	Single/without stable partnership
Sociable premorbid personality	Schizoid premorbid personality
Good premorbid adjustment	Poor premorbid adjustment
Psycho-reactive trigger of onset	Genetic risk
Acute onset of symptoms	Chronic onset of symptoms
Affective symptoms at onset	Negative symptoms at onset
Low level of "Expressed Emotions" in family	High level of "Expressed Emotions" in family
Living in developing countries	Living in industrialized countries

Can we predict the course of the disease?

Are there characteristics which can help predict the course a patient's illness will take? Many such "predictors" have been found in different studies. Table 3 shows some of those most frequently mentioned.

Genetic risk/psychological burden. According to many studies, a patient who has no familial risk and whose illness was brought on by a strong psychological burden has a favourable prognosis (reviews e.g. McGlashan 1988; Huber et al. 1979; Hubschmid and Ciompi 1990). However, patients who have a family history of schizophrenia and/or for whom the illness was not triggered by any recognizable factor are obviously faced with a less favourable prognosis. Although these findings seem very plausible in the frame of the vulnerability model, there are also contradictory findings, and methodologically sound studies examining the influence of genetic risk on course and outcome are not known to the authors.

Gender. Women seem to have a more favourable course than men (for reviews see Flor-Henry 1985; Seeman 1986; Hogarty 1988; Angermeyer et al. 1989). Most studies thus far have shown that women have fewer and shorter hospital stays, show better social adjustment and have a better living situation than men, whereas the symptom-related course seems to be similar for both genders (e.g. Tsuang and Fleming 1987; Shepherd et al. 1989; Flor-Henry 1985). Women's mortality is also lower (see above).

These gender differences have also been regarded in more recent studies with sound methodology. Thus, for example, Salokangas and Stengård (1990) in their follow-up study of first-admitted patients found a poorer psychosocial outcome in men with more negative symptoms and depression as well as poorer working capacity and functional abilities after 2 years. In the WHO DOS study (Jablensky et al. 1992) first-contact women tended to have a better outcome in terms of the pattern of course, percentage of time psychotic, percentage of time in complete remission, percentage of time of unimpaired social

functioning and, finally, percentage of time in hospital. In the Nottingham subsample of the DOS study female gender in a multiple linear regression together with age, ever married, acuteness of onset and length of untreated illness predicted a more favourable 13-year outcome as regards a whole range of outcome measures (Harrison et al. 1996). However, this was not the case anymore, when analyses were restricted to the restrictive diagnostic classification CATEGO-S+ (Wing et al. 1974), i.e. mainly to patients with first-rank symptoms.

Quite similar were the results of the previously mentioned Danish case-register study on schizoprenic and paranoid psychoses. Time in hospital during the 10-year course was analysed (Häfner et al. 1991; Riecher et al. 1991; Maurer 1995). Only by also taking those with paranoid disorders into account did the men on average have a longer overall length of stay (see above). When the analysis was limited to those with schizophrenic disorders, which are very narrowly defined in Denmark, no significant gender differences were discovered any more. There is also a long list of studies, compiled by Avison and Nixon-Speechly (1987), which found no gender differences as far as course is concerned.

Thus, the findings are not unequivocal. But most studies indicate that, at least if a relatively broad diagnostic definition of schizophrenia is used, the course of schizophrenia seems to be better in women than in men. Possible reasons for this could be men's poorer compliance (Hogarty 1988), their poorer response to neuroleptics (Seeman 1986), the fact that their premorbid adjustment is already poorer than that of women (Goldstein 1988), or, as suggested by Vaughn et al. (1984), their higher susceptibility to Expressed Emotions (EE).

Seeman (1986) suspects that the antidopaminergic effect of the female sex hormone oestradiol accounts in part for the women's better outcome. Well in accordance with this is a finding of several studies with very long observation periods. They report that the superior overall functioning of women is attentuated over time, and that there is a change for the worse especially around menopause (e.g. Opjardsmoen 1991; Retterstøl 1991). Based on Danish case-register data it was recently shown that the institutional course of women with *late-onset* schizophrenia is worse than that of late-onset men (Riecher-Rössler et al. 1997). In connection with other results which point to oestrogens having a protective effect in schizophrenia (Häfner et al. 1993b, 1998; Riecher-Rössler and Häfner 1993; Riecher-Rössler et al. 1994a, b), these findings could indicate that the course of this disease is better only in young women with a high physiological production of oestradiol, and that the decline in the oestradiol level around menopause leads to a worsening in course.

Another important explanation for gender differences in course probably has to do with the differences in age of onset for the genders. As the ABC study (Häfner et al. 1991, 1993b) showed, men become ill on average 3–4 years earlier than women. Whereas men on average begin to show the earliest signs of a mental disturbance at age 24.3 years, women are on average 27.5 years of age. The first psychotic symptomatology appears in men on average at age 26.4 years and in women at 30.1 years. This means that at the point when the illness enters the person's social biography, women have already achieved more stability than men in their various social roles (education, job, partnership, income, etc.); (Häfner et al. 1993b, 1998; Fätkenheuer 1992). And good social adjustment before the first hospitalization is an important predictor of – at least socially – a good course.

Age. In general, a young age at onset of illness is considered to be a predictor of unfavourable course; however, the findings are somewhat inconsistent (reviews e.g. McGlashan 1988; Retterstøl 1987; Watt and Szulecka 1979).

The WHO DOS study, with an upper age limit of 54 years, compared those under age 25 years with those over 25 years. During the 2-year follow-up, the "older" patients spent less time in hospital and experienced social impairment for shorter periods of time than their younger counterparts.

Most studies on late-onset schizophrenia, i.e. the patient group with onset after age 40 or 45 years, also suggest a better prognosis for these patients in comparison with those with an early onset (e.g. Bleuler 1943; Huber et al. 1975; Marneros et al. 1992) – however, not without contradiction (e.g. Hinterhuber 1973). Own analysis of data from the Danish case-register similarly showed a better 10-year course for those first hospitalized after 40 years of age in comparison with those hospitalized earlier, as concerns parameters such as number and length of inpatient stays. Especially the older men had a comparatively better course. In women there was no such positive effect of age, possibly because of the waning of the protection by oestrogens (Riecher-Rössler et al. 1997).

The better course of late – as opposed to early-onset patients could be due to a variety of factors such as their probably lower genetic risk (Harris and Jeste 1988; Riecher-Rössler et al. 1997), their better premorbid social adjustment (see above) and the waning of the activity of the dopominergic system in the eldery as suspected by some authors (Morgan 1992).

Family status. Patients already married at the onset of illness can also expect a better course (reviews e.g. McGlashan 1988; Huber et al. 1979). In the WHO DOS study (Jablensky et al. 1992), patients who were married at illness onset had a better 2-year outcome in terms of all clinical and social measures assessed. However, it must be kept in mind that, "marital status" is confounded by other variables which also influence prognosis, especially age and gender. It was shown, for example, that the single schizophrenic patients are in most cases young males (Riecher et al. 1989; Riecher-Rössler et al. 1992). Therefore, it remains unclear whether their poorer prognosis can indeed partly be accounted for by their marital status or whether it has to do solely with the fact that these patients are mainly early-onset men, who per se have a less favourable prognosis (see above). In many predictor studies such a confounding of variables was not controlled.

Acuteness of illness onset. Another negative predictor seems to be an insidious, chronic development of the disease as opposed to an acute onset (reviews e.g. McGlashan 1988; Ram et al. 1992; Huber et al. 1979; Hubschmid and Ciompi 1990). However, the results were often not based on first-admitted patients, and the actual onset of the disease was often not examined thoroughly. The WHO DOS study (Jablensky et al. 1992) was one of the studies that examined first-episode schizophrenic patients. Here, the type of onset (acute, subacute or insidious) was also one of the most important predictors of the 2-year course. But "acute" was very narrowly defined: patients who developed their psychotic symptoms within more than 1 month(!) showed the poorest prognosis. And, as was shown in the ABC study, the mean time from the first psychotic symptom until the maximum of psychotic symptomatology is as long as 1.6 years (Zedlick et al. 1993). In light of these results it seems that the early course of the disease should be looked at more thoroughly in future studies in order to operationalize "acuteness of onset" more exactly.

Symptomatology and diagnosis at illness onset. Relationships were also established between the initial symptomatology and the later course. For instance, blunted affect or other negative symptoms at an early point in the course of illness was described as unfavourable but initial depression as favourable (McGlashan 1988; Ram et al. 1992; Huber et al. 1979). Whereas catatonic and paranoid clinical pictures at onset were thought to be favourable, hebephrenic symptomatology seemed to predict a less favourable course (review e.g. McGlashan 1988; Retterstøl 1987).

Recent studies with sound methodology have thus far not unequivocally confirmed these results. In the WHO DOS study (e.g. Jablensky et al. 1992), those diagnosed with hebephrenic and paranoid subtypes of schizophrenia had the least favourable course and a diagnosis of "acute schizophrenic episode" had the best prognosis. This result, however, is highly confounded with the acuteness of onset.

In the DOS study it was also differentiated between narrow and broad diagnostic definitions. Surprisingly, the course of "nuclear schizophrenia", which was defined predominantly by Schneider's first-rank symptoms, was hardly worse than that of the more broadly defined diagnostic group.

However, it is clearly important which diagnostic system is used. For example, patients who were classified as schizophrenic according to DSM-III or the Feighner Criteria (Feighner et al. 1972) have a worse course, as far as symptoms are concerned, than those diagnosed according to ICD-9 or the Research Diagnostic Criteria (RDC; Spitzer et al. 1978; review e.g. by Ram et al. 1992). This is obviously due to the fact that DSM-III and the Feighner Criteria require a period of illness of at least 6 months before the diagnosis "schizophrenia" can be given. Patients who remit more quickly, thus likely representing a selection of those with good prognosis, would not be diagnosed as schizophrenic in the first place according to these systems. This means that DSM-III or Feighner schizophrenics, as compared with ICD-9 or RDC schizophrenics, represent a selection of more severely ill patients with correspondingly poorer course.

"Premorbid" adjustment and personality. "The more successful the social adjustment up to the outbreak of illness and the more harmonious the premorbid personality, the greater the chance statistically of a favourable course" – this was the conclusion drawn by Retterstøl (1987; p. 96) in his review of literature. However, in light of more recent research, this statement needs to be discussed. As shown previously, the so-called poor premorbid adjustment is likely, at least in part, an early indicator of illness (Häfner et al. 1991); thus, part of this prediction in essence probably means that a poor early course predicts a poor further course.

Expressed emotions. Based on various studies with cohorts of consecutively admitted patients, a prevailing surplus of emotionality as defined by the Expressed Emotions (EE) concept was identified as a negative predictor (Brown et al. 1972; Vaughn et al. 1984). Later studies on first-admitted patients, however, were less convincing with reference to this category (e.g. MacMillan 1986). In a follow-up of a subsample of the Chandigarh (India) cohort of first-contact schizophrenic patients from the WHO Determinant of Outcome Project, Leff et al. (1990) found that the global EE index at initial interview did not predict relapse over 2 years. They only found initial hostility to be a significant negative predictor. Furthermore, EE have often not been taken as a simple predictor only, but also as an influencing factor, a causal interpretation which has been questioned e.g. by Goldstein et al. (1994). They suggest that a complex transactional model best explains the connection between high EE status of a relative and the risk for patient relapse. Recently, Schulze-Mönking et al. (1997) showed that the EE effect was independent of patients and parents living together, which is a strong argument against a simple causal interpretation of the connection between EE and the course of schizophrenia.

Transcultural aspects. In the transcultural WHO DOS study (Jablensky et al. 1992) an additional important predictor was presented. Patients in developing countries had a significantly better prognosis than patients in industrialized countries, both in terms of their symptomatology as well as with regard to their social level of functioning. This finding has sparked a great deal of discussion, but no one has yet come up with a fully adequate explanation for it. Edgerton and Cohen (1994) even came to the conclusion that there is no sufficient evidence to support a more favourable course in developing countries.

Other predictors. Numerous other predictors have also been mentioned in the literature, e.g. other sociodemographic factors and personality characteristics, neuropathological abnormalities, such as enlarged cerebral

ventricles, cognitive deficits, neurological soft signs or perinatal complications, etc. (e.g. Ciompi and Müller 1976; Huber et al. 1979; Strauss and Carpenter 1977; Andreasen 1982; Crow et al. 1982; Möller and von Zerssen 1986; Leff 1991; Hubschmid and Ciompi 1990; Wilcox and Nasrallah 1987; Andreasen et al. 1986). According to our knowledge, however, none of these predictors have thus far been confirmed by long-term follow-up studies meeting the above-named methodological standards. Apart from this, it is often not clear whether the abnormalities reported are cause or consequences of the disease and/or the treatment (Lieberman et al. 1996).

On the whole, research on predictors obviously suffers from the same methodological problems as research on course in general, because it is based on the same studies. In addition, there are other specific problems. As has been mentioned, the confounding of different predictors and their interaction has often not been taken into account. Research on predictors has also not always been completely free of seemingly tautological conclusions, e.g. the prediction of a further poor course based on certain indicators of a poor early course such as a poor "premorbid" adjustment (see above, also compare Häfner et al. 1991; Angst 1988). Finally, sometimes false causal conclusions have been arrived at by considering "predictors" to be equivalent to "influencing factors" An example of this is the finding that patients with high-EE families typically have a poorer course. This association can be interpreted as a high level of emotionality in the family has a negative influence on course. But it is also possible that the increased emotionality in such a family is a result of the member of this family being more severely ill than that of another family. In such a case a poor course would have to be explained, at least in part, by the severity of illness, and the high emotionality in the family would be less a cause than a result of the patient's very serious disease and severely disturbed behaviour (which does not rule out the value of an intervention aimed at reducing high EE, as this could break through the vicious circle of behavioral disturbances and high EE; for review see Leef 1994).

The case of marital status is similar; marriage (or stable partnership) is considered to be a factor indicating good prognosis. However, this does not necessarily mean that a steady partnership would have a positive influence on the course of illness. Instead, there are other factors to explain this association. Apart from the confounding of marital status with age and gender, we may assume that the more severely ill patients are less likely to find a steady partner, and that the prognosis is determined in at least equal measure by this illness factor as it is by marital status.

Thus, if a patient is suffering from a severe form of the disease, this is often already shown in the very early preclinical course of the disease in a wide range of areas through adjustment and behavioural problems at work, in the family as well as in other areas of contact. If these patients then go on to have a poor course of illness, this is at least in part a consequence of their comparatively severe illness, i.e. directly in the sense of the "natural" course as well as indirectly in terms of the unfavourable repercussions brought on by the illness-induced negative social situation. If such factors of confounding and interaction are not taken into consideration, predictors can at most be considered as risk indicators but certainly not as influencing factors.

In the hope of improving the ability to predict outcome, predictors have been combined in so-called prognostic scales (i.e. by Strauss and Carpenter 1974), even though only part of the variance of the later course can be predicted [20% (Gmuer 1986) to 80% (Vaillant 1964) have been mentioned, the very high latter percentage probably being due to partly tautological factors].

Has the course of schizophrenic disorders improved in the past 100 years?

One hundred years of schizophrenia research have also been 100 years of research on therapy. Thus, the final question to be asked is: Has the course of schizophrenia improved during these 100 years? Has the introduction of various new methods of therapy, which undoubtedly have improved the short-term course of the disease, also resulted in a better long-term course?

The first methods of treatment were discovered in the 1930s with the introduction of insulin coma therapy and electroshock therapy. In the 1950s a breakthrough in the treatment of schizophrenia was signaled with the introduction of chlorpromazine, the first neuroleptic. In the meantime, neuroleptics have proved to be most helpful, not only for therapy of acute psychotic episodes, but also for relapse prevention (Retterstøl 1987; Ram et al. 1992; Davis et al. 1980; Hogarty et al. 1976). Since the 1960s further effective treatment methods, such as certain psycho- and sociotherapeutic as well as rehabilitative measures, have increasingly been put into action, accompanied by deinstitutionalization and the improvement of community-based care (see e.g. Wing 1987; Leff et al. 1982; Hogarty et al. 1991; Stein and Test 1976; Wing 1988; Rössler et al. 1996).

In the meta-analysis previously mentioned, Hegarty et al. (1994) examined whether course and outcome underwent changes during these different time periods. They evaluated 320 studies with a total of 51,800 patients from the years 1895–1992. According to expectation, the proportion of improved patients was significantly higher in the second half of the century than it was in the first half. Whereas between 1895 and 1955 only 35% of patients were classified as "improved", from 1956 to 1985 this category accounted for 49% of patients. The past decade, however, has seen a drop in improved patients back to 36%.

The main reason for the improved course since the 1950s certainly has to do with improved treatment methods, especially the introduction of neuroleptics, but also the improvement in psychosocial care. This is partly confirmed by Wyatt (1991), who in an analysis of 22 follow-up studies has shown that an early prescription of neuroleptics increases the likelihood of a favourable course.

The most interesting finding of this meta-analysis, however, was how strongly "outcome" is dependent on the diagnostic system in use. After an initial era in which schizophrenia was narrowly defined according to the Kraepelinian concept in which chronicity was determining the diagnosis of Dementia praecox, in the 1930s and 1940s Bleuler's broader and more cross-sectional concept of the illness became dominant. Only recently, with the introduction of the "6-month criterion" as part of the Feighner Criteria (1972) and the DSM-III criteria, has there been a return to a more narrow, course-oriented "neo-Kraepelinian" diagnosis. The trend of the past decade toward a once again poorer course likely corresponds in part to this return to a course-oriented diagnosis. When chronicity again – as in Kraepelin's time – is a prerequisite for the diagnosis of schizophrenia and studies are only examining patients with an illness duration of at least 6 months, patients with a very favourable course are missed and the results of these studies are correspondingly pessimistic. These developments at the same time show the importance of diagnostic convention which is obviously constitutive for the ensuing results on course.

A further cause of the recent downward trend is probably the fact that due to deinstitutionalization and improved outpatient treatment, it is increasingly only the more chronic and severely ill patients who are being hospitalized and, as studies continue to be based on hospital samples, examined.

Conclusion

Although 100 years have passed since it was first described as "Dementia praecox", there has been no great gain in definite knowledge on the course of schizophrenic psychoses. As this review shows, the main reason for this is that most studies suffer from more or less serious methodological shortcomings, which do not allow for a generalization of results. McGlashan (1988) expressed it in the following manner. "… follow-up studies have taught us a great deal about schizophrenia thus far. Most important, they have taught us how to construct future studies that maximize a return of meaning" (p. 538).

As a consequence of this, there are not many universally applicable statements which can be made about the course of schizophrenic psychoses. Some points, however, seem to be clear: this disease is not a "Dementia praecox". The illness appears not to follow a course of progressive deterioration as Kraepelin had thought in the beginning. Instead, even after years or decades, significant improvement is not impossible. Nevertheless, schizophrenic psychoses appear to take a more difficult course than do other functional psychoses. The course is also often fatal, due primarily to the greatly increased risk of suicide. It also seems to become increasingly clear that the illness process probably often begins long before first admission with a schizophrenia diagnosis and probably even long before the first occurrence of psychotic symptomatology. The beginning is obviously often marked by unspecific signs only and a so-called break in the lifeline (Knick in der Lebenslinie) as already described by early psychiatrists. This finding is intriguing because it could potentially, as in other diseases, show a way to early diagnosis and therapy, with further improvement of the long-term outcome.

It also seems to be clear that the course of these psychoses is far from uniform. On the contrary, very different types of course ranging from complete cure to severely disabling chronic forms are found. Some patients apparently experience only one episode of illness and are afterwards more or less fully recovered. Another group of patients has several episodes. with no or little disability between episodes. Many patients, however, suffer from chronic symptoms of a more or less severe degree. As this review shows the proportions of patients in both extreme groups have thus far been underestimated: on the one hand, patients with very good prognosis have been underrepresented in previous studies on the basis of hospital prevalence samples and also in recent studies using the 6-month criterion for diagnosis. On the other hand, also patients with very severe courses – namely the refusers of studies and the many patients who committed suicide – have often not been adequately taken into consideration when assessing the course of schizophrenic psychoses.

There is obviously a marked heterogeneity of courses which implies that schizophrenic psychoses are possibly, as many psychiatrists have always believed, not a single, aetiologically uniform disease, but rather a *group* of diseases with different aetiologies and correspondingly different courses. Fairly reliable predictions of the course can hardly be identified presently. This has probably not only to do with the methodological deficits of previous studies, but also with the heterogeneity of this group of diseases.

Finally, it is probably safe to state that the course of schizophrenia has improved considerably since Kraepelin's time. This is difficult to substantiate with numbers and rough categories, as the meta-analysis by Hegarty et al. (1994) shows, but becomes very clear when the case descriptions from then and now are examined comparatively. Even if some symptom-related aspects of long-term course might not have met the euphoric expectations of the 1960s and 1970s especially as regards the often observed chronic course of negative symptoms, it is evident that modern therapeutic possibilities have contributed to a marked reduction in acute psychotic episodes and to decisive improvements in the social aspect of course, and hopefully also to an improved quality of life for people with schizophrenic psychoses and their relatives.

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